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Lidocaine and Mexiletine Inhibit Mitochondrial Oxidation in Rat Ventricular Myocytes

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Background: **Accumulating evidence suggests that mitochondrial rather than sarcolemmal adenosine triphosphate–sensitive K^+ (K_{ATP}) channels may have an important role in the protection of myocardium during ischemia. Because both lidocaine and mexiletine are frequently used antiarrhythmic drugs during myocardial ischemia, it is important to investigate whether they affect mitochondrial K_{ATP} channel activities.**

Methods: **Male Wistar rats were anesthetized with ether. Single, quiescent ventricular myocytes were dispersed enzymatically. The authors measured flavoprotein fluorescence to evaluate mitochondrial redox state. Lidocaine or mexiletine was applied after administration of diazoxide (25 μM), a selective mitochondrial K_{ATP} channel opener. The redox signal was normalized to the baseline flavoprotein fluorescence obtained during exposure to 2,4-dinitrophenol, a protonophore that uncouples respiration from ATP synthesis and collapses the mitochondrial potential.**

Results: **Diazoxide-induced oxidation of flavoproteins and the redox changes were inhibited by 5-hydroxydecanoic acid, a selective mitochondrial K_{ATP} channel blocker, suggesting that flavoprotein fluorescence can be used as an index of mitochondrial oxidation mediated by mitochondrial K_{ATP} channels. Lidocaine (10^{-3} to 10 mM) and mexiletine (10^{-3} to 10 mM) reduced oxidation of the mitochondrial matrix in a dose-dependent manner with an EC_{50} of 98 ± 63 μM for lidocaine and 107 ± 89 μM for mexiletine.**

Conclusions: **Both lidocaine and mexiletine reduced flavoprotein fluorescence induced by diazoxide in rat ventricular myocytes, indicating that these antiarrhythmic drugs may produce impairment of mitochondrial oxidation mediated by mitochondrial K_{ATP} channels.**

CARDIAC myocytes and other cells have adenosine triphosphate (ATP)–sensitive K^+ (K_{ATP}) channels in the inner mitochondrial membrane, which respond to many of the same openers and blockers as do the sarcolemmal channels.[1–4] Although the physiologic roles of mitochondrial K_{ATP} channels in cardiac myocytes remain unclear, mitochondrial rather than sarcolemmal K_{ATP} channels may be more important for the protection of myocardium during ischemia. Garlid *et al.*[5] reported that mitochondrial K_{ATP} channels mediate cardioprotection produced by K_{ATP} channel openers. The results of recent studies support this hypothesis.[6–10]

Lidocaine and mexiletine are antiarrhythmic drugs used most frequently for treatment of ventricular arrhythmias during myocardial ischemia. We previously reported that the effects of lidocaine on Na^+ channel activities[11] are similar to those of mexiletine,[12] but recent studies suggest that these drugs have different effects on sarcolemmal K_{ATP} channel activities. Lidocaine inhibits,[13,14] whereas mexiletine inhibits,[15] does not affect,[16] or activates[17] sarcolemmal K_{ATP} channels. To determine whether lidocaine and mexiletine affect mitochondrial oxidation mediated by mitochondrial K_{ATP} channels, we measured flavoprotein fluorescence in isolated rat ventricular myocytes.

Materials and Methods

Preparation of Cardiac Ventricular Myocytes

This study was approved by the Animal Investigation Committee of Tokushima University (Tokushima, Japan) and followed the animal use guidelines of the American Physiological Society (Bethesda, MD). Forty-eight male Wistar rats (250–300 g) were anesthetized with ether, and 1.0 IU/g heparin was injected intraperitoneally 30 min before surgery. Myocytes were obtained enzymatically (0.2 mg/ml collagenase and 0.05 mg/ml protease) using a Langendorff apparatus. The enzymatic dissociation method was similar to that of our previous study.[18]

Flavoprotein Fluorescence Measurement

Rod-shaped, clear striated ventricular myocytes were cultured on laminin-coated coverslips in M199 culture medium with 5% fetal bovine serum at 37°C. Experiments were performed during the next day. The mitochondrial redox state was monitored by recording the fluorescence of flavin adenine nucleotide-linked enzymes in mitochondria and served as an index of mitochondrial K_{ATP} channel activities. Myocytes were superfused with bath solution containing 140 mM NaCl , 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 10 mM HEPES (pH adjusted to 7.4 with NaOH) at room temperature (20 ± 2°C). Fluorescence was monitored microscopically (Eclipse TS100; Nikon, Tokyo, Japan) with a digital charge coupled device camera (ORCA; Hamamatsu Photonics, Hamamatsu, Japan) from one cell at a time by focusing on individual myocytes. Fluorescence of single cells was excited for 100 ms every 10 s. Excitation of flavoprotein was obtained from a Xenon arc lamp fil-

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tered at 450–490 nm and reflected to the microscope objective lens (×40) by a dichroic mirror centered at 505 nm. Emitted fluorescence was recorded to pass through the dichroic mirror to a 520-nm-long path filter and was stored on a computer. The redox signal images were analyzed for average pixel intensities of regions of interest on a myocyte using an image processing system (AQUACOSMOS; Hamamatsu Photonics). The change of fluorescence was normalized to the baseline flavoprotein fluorescence obtained after exposure to 5 μM 2,4-dinitrophenol (DNP), a protonophore that uncouples respiration from ATP synthesis and collapses the mitochondrial potential, at the end of the experiments. At least 30 normalized fluorescence images were averaged before (diazoxide alone) and at each concentration of drugs. In the first series of the experiments, the effects of diazoxide, a selective mitochondrial K_{ATP} channel opener,[6] and 5-hydroxydecanoic acid sodium (5-HD), a relatively selective mitochondrial K_{ATP} channel blocker, on flavoprotein fluorescence were evaluated. Then we assessed the effects of diazoxide alone and in combination with lidocaine or mexiletine on flavoprotein fluorescence in the following series. In the same cell, flavoprotein fluorescence was recorded before (diazoxide alone) and at five concentrations of either lidocaine ($10^{-3} \sim 10$ mM) or mexiletine ($10^{-3} \sim 10$ mM). Six data points obtained in the same cell were plotted as drug concentration compared with the normalized flavoprotein fluorescence; then these data were converted to probits, and the concentration–response equation was calculated by least-square curve fitting. From this equation, the concentrations of lidocaine or mexiletine needed to induce 50% inhibition of diazoxide-induced flavoprotein oxidation (EC_{50}) were calculated in each cell.

Drugs

Lidocaine and mexiletine were obtained from Sigma Chemical (St. Louis, MO). Diazoxide (Sigma) was dissolved in dimethyl sulfoxide (< 0.1%) and prepared as a stock solution. 5-HD was purchased from Biomol Research Laboratories (Plymouth Meeting, PA). All other solutions were made daily.

Statistical Analysis

Data are expressed as mean ± SD. Differences among data sets were evaluated by analysis of variance followed by Student-Newman-Keuls *post hoc* test. A *P* value less than 0.05 was considered significant.

Results

Effects of Diazoxide and 5-HD on Mitochondrial K_{ATP} Channels

Figure 1 shows the representative example of flavoprotein fluorescence in cells exposed to diazoxide and 5-HD. The flavoprotein fluorescence value was expressed as a percent of that exposed to 5 μM DNP at the end of the experiments (DNP value). Diazoxide (25 μM) caused reversible mitochondrial oxidation to 63 ± 19% of the DNP values (n = 7). 5-HD (100 μM) attenuated the oxidative effects of diazoxide to 2 ± 5% of the DNP value ($P < 0.05$ *vs.* diazoxide, n = 7). After washout of these drugs, mitochondrial oxidation was restored to the baseline level.

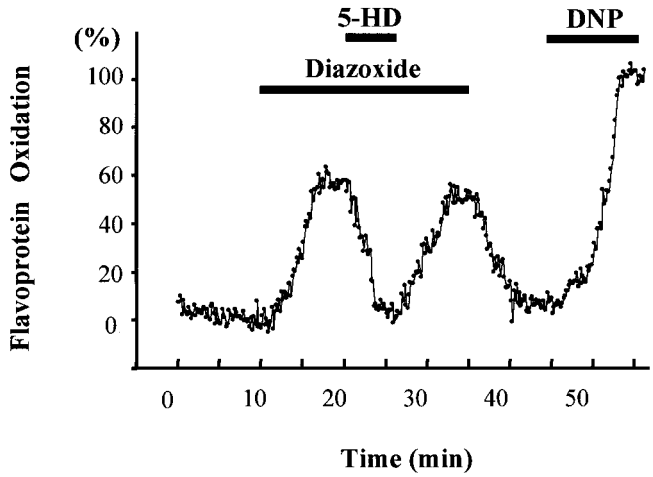

Fig. 1. The effects of diazoxide alone or in combination with 5-hydroxydecanoic acid (5-HD) on flavoprotein fluorescence. Diazoxide (25 μM) induced a reversible increase of mitochondrial oxidation (n = 7). 5-HD (100 μM) significantly attenuated the oxidative effects of diazoxide. After washout of diazoxide, mitochondrial oxidation was restored to the baseline level. The redox signal was normalized to the baseline flavoprotein fluorescence obtained during exposure to 5 μM 2,4-dinitrophenol (DNP) at the end of the experiments.

Effects of lidocaine on Mitochondrial K_{ATP} Channels

Figure 2 shows the relation between lidocaine concentration and diazoxide (25 μM)-induced flavoprotein oxidation (n = 7). Flavoprotein oxidation was 63 ± 5% in the presence of diazoxide alone. With lidocaine, flavoprotein oxidation was 63 ± 7% at 0.001 mM, 42 ± 14% at 0.01 mM ($P < 0.05$ *vs.* diazoxide alone), 25 ± 7% at 0.1 mM ($P < 0.05$), 9 ± 9% at 1 mM ($P < 0.05$), and 1 ± 1% at 10 mM ($P < 0.05$). Lidocaine induced 50% inhibition of diazoxide-induced flavoprotein oxidation (EC_{50}) at 98 ± 63 μM concentration.

Effects of Mexiletine on Mitochondrial K_{ATP} Channels

Figure 3 shows that mexiletine, like lidocaine, reduced the diazoxide-induced oxidation of flavoproteins in a concentration-dependent manner. Flavoprotein oxidation was 64 ± 6% in the presence of diazoxide alone. With mexiletine, flavoprotein oxidation was 61 ± 8% at 0.001 mM, 51 ± 5% at 0.01 mM ($P < 0.05$ *vs.* diazoxide alone), 34 ± 10% at 0.1 mM ($P < 0.05$), 23 ± 5% at 1 mM

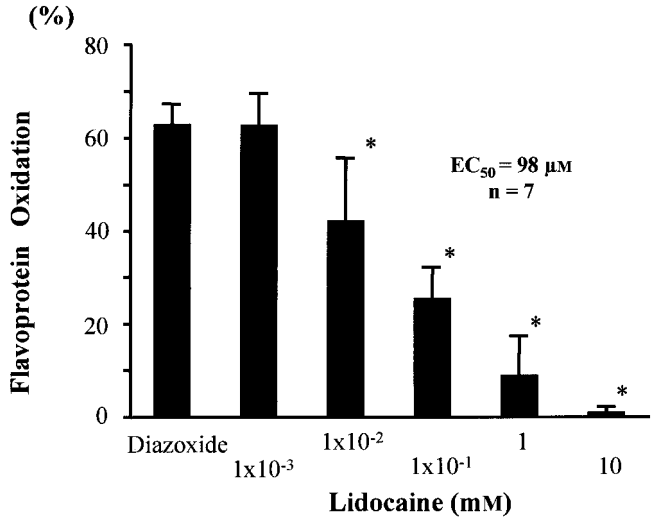

Fig. 2. Concentration-dependent effects of lidocaine on diazoxide (25 μM)-induced flavoprotein oxidation. The redox signal was normalized to the baseline flavoprotein fluorescence obtained during exposure to 5 μM 2,4-dinitrophenol (DNP) at the end of the experiments. Each bar constitutes measurements from seven single ventricular myocytes. *$P < 0.05$ *versus* diazoxide alone.

($P < 0.05$), and 1 ± 4% at 10 mM ($P < 0.05$; fig. 3B; n = 10). The EC_{50} for mexiletine to induce 50% inhibition of diazoxide-induced flavoprotein oxidation was 107 ± 89 μM.

Discussion

The major findings in the current study are that both drugs inhibit diazoxide-induced flavoprotein fluorescence, which correlates with mitochondrial oxidation and depolarization. Activation of K_{ATP} channels produces cardioprotective effects in cardiac myocytes,[19] but the underlying mechanisms for such cardioprotection are poorly understood. One early hypothesis proposed that opening sarcolemmal K_{ATP} channels shortens the action potential duration and then depresses contractility,[19,20] which is a major source of $_{ATP}$ consumption. Recent evidence, however, contradicts this hypothesis. Yao and Gross[21] found that a low dose of the K_{ATP} channel opener bimakalim had a minimal effect on action potential duration but still reduced infarction size. Such dissociation has also been shown in other studies.[22–25] These data suggest that abbreviation of action potential duration may not be necessary for cardiac protection. The opening of mitochondrial rather than sarcolemmal K_{ATP} channels may be a major contributor to cardiac protection against ischemia.[5] Although the physiologic and pathophysiologic roles of the mitochondrial K_{ATP} channel are not yet clear, opening mitochondrial K_{ATP} channels results in K^+ entry and intramitochondrial depolarization.[1] Therefore, a possible mechanism for the cardioprotective action of mitochondrial K_{ATP} channels is that dissipation of inner mitochondrial membrane potential decreases the driving force for Ca^{2+} influx through the Ca^{2+} uniporter.[6] This would reduce mitochondrial Ca^{2+} overload and cause matrix swelling, which has been shown to enhance ATP synthesis and stimulate mitochondrial respiration.[6] Another possibility is that opening mitochondrial K_{ATP} channels, by decreasing the membrane potential, could promote binding of the endogenous mitochondrial ATPase inhibitor[26] and thus conserve ATP during ischemia.

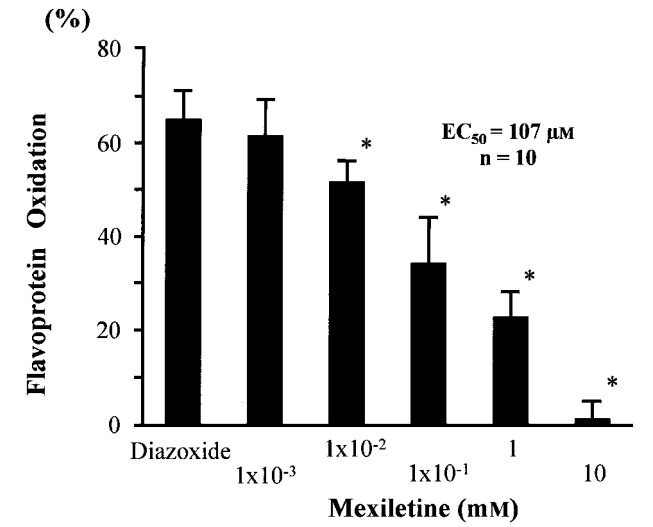

Fig. 3. Concentration-dependent effects of mexiletine on diazoxide (25 μM)-induced flavoprotein oxidation. The redox signal was normalized to the baseline flavoprotein fluorescence obtained during exposure to 5 μM 2,4-dinitrophenol at the end of the experiments. Each bar constitutes measurements from 10 single ventricular myocytes. *$P < 0.05$ *versus* diazoxide alone.

The mitochondrial redox state can be monitored by recording the fluorescence of flavin adenine nucleotide–linked enzymes in the mitochondria.[27,28] To test the hypothesis that mitochondrial K_{ATP} channels have an important role in cardioprotection, Liu *et al.*[6] examined the effects of diazoxide on both mitochondrial and sarcolemmal K_{ATP} channel activities using flavoprotein fluorescence, an index of mitochondrial redox state, and sarcolemmal K_{ATP} currents as indicators in intact rabbit ventricular myocytes and showed that diazoxide induced reversible oxidation of flavoproteins but did not activate sarcolemmal K_{ATP} channels. They also found that diazoxide decreased the rate of cell death in a cellular model of simulated ischemia to approximately half that of controls. They concluded that diazoxide targets mitochondrial but not sarcolemmal K_{ATP} channels and that the opening of mitochondrial rather than sarcolemmal K_{ATP} channels might contribute to cardiac protection against ischemia.[6] These results are similar to those obtained in the current study. We also studied the effects of diazoxide alone or in combination with 5-HD on flavoprotein oxidation in isolated rat ventricular myocytes and found that diazoxide caused reversible mitochondrial oxidation and that 5-HD attenuated the oxidative effects of diazoxide (fig. 1). Therefore, the results reported by Liu *et al.*[6] and the results of the current

study led us to conclude that the flavoprotein fluorescence we measured reflects the redox state of mitochondria.

In the current study, both lidocaine and mexiletine reduced diazoxide-induced oxidation of flavoprotein in a concentration-dependent manner, suggesting that both drugs attenuate mitochondrial K_{ATP} channel activities. If the opening of mitochondrial rather than sarcolemmal K_{ATP} channels contributes to cardiac protection against ischemia, blockade of mitochondrial K_{ATP} channels by lidocaine and mexiletine may produce impairment of mitochondrial oxidation mediated by mitochondrial K_{ATP} channels. That is, our results suggest that both drugs may attenuate cardioprotective effects of mitochondrial K_{ATP} channels. In contrast, blockade of sarcolemmal K_{ATP} channels by lidocaine and mexiletine may be advantageous in the prevention of arrhythmia. During myocardial ischemia, extracellular myocardial K^+ concentration in the ischemic zone increases, and the resultant slowing of impulse propagation has a pivotal role in the pathogenesis of ventricular arrhythmia.[29] In heart cells, K_{ATP} channels are activated by depletion of intracellular ATP, hypoxia, or exposure to metabolic inhibitors[18] and cause an increase in K^+ efflux. The activation of K_{ATP} channels is at least partially responsible for the increase in outward K^+ currents, shortening of action potential duration, and increase in extracellular K^+ concentration during anoxic or globally ischemic conditions.[30–32] Bekheit *et al.*[30] reported that glibenclamide, a K_{ATP} channel blocker, decreases the K^+ loss from ischemic myocardium and reduces the incidence of arrhythmia. These findings suggest a significant contribution of sarcolemmal K_{ATP} channels to the formation of cardiac arrhythmia during ischemia.[30–33]

Both lidocaine and mexiletine are known to exert their therapeutic effects by selectively blocking voltage-dependent Na^+ channels in a rate- and concentration-dependent manner.[11,12] In addition, many reports have evaluated the effects of these drugs on sarcolemmal K_{ATP} channel activities. Using voltage clamp techniques, Yoneda *et al.*[13] reported that lidocaine inhibits K_{ATP} channel activities in a concentration-dependent manner in *Xenopus* oocytes. Using patch clamp techniques, Olschewski *et al.*[14] also reported that lidocaine blocked K_{ATP} channels in rat cardiomyocytes (EC_{50} = 43 μM). In contrast, the effects of mexiletine on K_{ATP} channel activities are controversial. Tricarico *et al.*[15] reported that mexiletine was a state-dependent K_{ATP} channel inhibitor in skeletal muscle. In ventricular muscles, Wu *et al.*[16] found that 30 μM mexiletine did not significantly affect K_{ATP} current, whereas Sato *et al.*[17] reported that mexiletine shortened action potential duration *via* partial activation of K_{ATP} channels.

In the current study, the EC_{50}s for both lidocaine and mexiletine were higher than those in clinical use. The EC_{50}s obtained in the current study were 98 μM for lidocaine and 107 μM for mexiletine, whereas the therapeutic ranges of plasma concentration of lidocaine and mexiletine used as antiarrhythmic drugs have been reported as approximately 5–30 and 2–9 μM, respectively.[34–36] In addition, we studied the effects of drugs in isolated rat ventricular myocytes. The effects of these drugs on rat myocardium may be different from the effects on human myocardium. Therefore, we should be careful in extending the current results to the human heart.

In conclusion, both lidocaine and mexiletine reduced flavoprotein fluorescence induced by diazoxide in rat ventricular myocytes, indicating that these antiarrhythmic drugs may produce impairment of mitochondrial oxidation mediated by mitochondrial K_{ATP} channels.

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